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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/898,887	07/03/2001	Raghavan Rajagopalan	MRD-61	2188

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EXAMINER	
LUKTON, DAVID	
ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 09/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/898,887	RAJAGOPALAN ET AL.	
	Examiner	Art Unit	
	David Lukton	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *15-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Pursuant to the directives of the response filed 6/21/05, claims 15 and 37 have been amended. Claims 15-46 remain pending. Applicants arguments filed 6/21/05 have been considered and found not persuasive.

✧

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 15 now recites (last 3 lines of the claim) that the target tissue is exposed to light such that the tissue itself is "photosensitized". However, there does not appear to be support for this. Certainly, the specification is replete with recitations of the word "photosensitizer". In addition, the following passage is noted (page 3, line 15+):

> "Type 1 mechanisms involve direct energy or electron transfer from the photosensitizer to the cellular components thereby causing cell death. Type 2 mechanisms involve two distinct steps, as shown in the following scheme…"

However, there does not appear to be descriptive support for the term "photosensitize" as a verb. This is more than a trivial grammatical observation. The term "photosensitize" is being used as a transitive verb in conjunction with the term "target tissue". It is not clear what chemical or biochemical process the term in question is intended to convey; in any case there is no description of the phrase in question.

✦

Claims 15-46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method of performing a "photosensitizing procedure".

As explained in a declaration filed 2/25/05, applicants demonstrated a modest effect on the viability of Lewis carcinoma cells *in vitro* in the presence of the compound *para*-nitrophenyl-*tert*-butyl sulfenate. In the presence of the compound and light, there was a slight decrease in cell viability. It is noted that the compound which was tested does not fall within the scope of the claimed invention. Thus, the first question is whether one could expect similar results *in vitro*, in the event that one of the proteins encompassed by substituent variable "E" were to be conjugated with the sulfenate compound that was tested.

A second issue concerns the matter of "administering to a target tissue". The claims encompass administering the compound to the subject orally, by injection and topically, for example. Thus, for example, if a tumor is present in the pancreas, would sufficient compound reach the pancreas to "photosensitize the target tissue"...? And would a quantity of 500 micrograms sulfenate compound per gram of pancreas actually reach the pancreas as suggested by claim 30...? Third, applicants have not actually demonstrated that photosensitization occurs when the sulfenate compound is combined with the Lewis carcinoma cells. The results could be explained by a simple homolytic bond scission (as disclosed in Pasto, *Tet. Lett* **35**, 4303, 1994) followed by abstraction of hydrogen atoms from lipid molecules (of the carcinoma cells) or membrane-bound proteins on the cells. This is not the same as a type I or a type II photosensitization reaction.

With regard to the first point, consider, for example, Bonnett R (*Journal of photochemistry and photobiology. B, Biology*, (1990 Jun) 6 (1-2) 29-37). As discussed therein, compound 7 exhibited considerable activity in a photonecrosis assay, whereas compounds 1-6 were not very effective. The point is that where photosensitization procedures are concerned, minor changes in structure can eliminate activity. Applicants are proposing to extrapolate from a result obtained with the compound *para*-nitrophenyl-*tert*-butyl sulfenate to compounds in which a protein has been conjugated thereto. What will be the effect of the protein on the photosensitization? One cannot

"predict" the outcome.

And even if applicants could show that a conjugate of e.g., neurotensin or cholecystokinin and *para*-nitrophenyl-*tert*-butyl sulfenate exhibited an effect on viability of Lewis carcinoma cells *in vitro* which is similar to that exhibited by the *para*-nitrophenyl-*tert*-butyl sulfenate itself, the next issue would be that of how to "administer" the conjugate to the target tissue. Consider, for example, the following types of cancer:

> breast cancer, prostate cancer, lung cancer, colon cancer, rectal cancer, bladder cancer, Non-Hodgkin Lymphoma, melanomas of the skin, cancer of the Kidney and Renal Pelvis, pancreatic cancer, oral cancer, esophagal cancer, ovarian cancer, thyroid cancer, stomach cancer, brain cancer, multiple myeloma, liver and intrahepatic bile duct cancer, acute myeloid leukemia, chronic lymphocytic leukemia, Hodgkin's Lymphoma, testicular cancer, intestinal cancer, chronic myeloid leukemia, acute lymphocytic leukemia, cancer of the vulva, gallbladder cancer, malignant mesothelioma, bone cancer, joint cancer, cancer of the hypopharynx, cancer of the eye, cancer of the nose, cancer of the ureter, cancer of the peritoneum, gastrointestinal carcinoid tumors, bladder cancer, melanoma, breast cancer, non-hodgkin's lymphoma, ovarian cancer, endometrial cancer, pancreatic cancer, kidney cancer (renal cell), prostate cancer, leukemia, non-melanoma cancer of the skin. Also included are sarcomas and carcinomas, such as the following: fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinoma, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, retinoblastoma, leukemia, lymphoma, multiple myeloma, Waldenströom's macroglobulinemia, and heavy chain disease.

For example, if one wants to perform a "photosensitizing procedure" on a patient with a liposarcoma, which "E" does one use? Is it a neurotensin receptor binding molecule, or a steroid receptor binding molecule? And if so, which one? Or suppose the patient is suffering from a medullary carcinoma. Does one use a "carbohydrate receptor binding molecule", and if so, which carbohydrate, and which molecule? The specification provides no guidance in this regard. And even if the specification had provided some sort of speculation as to which "E" moieties to use in which circumstances, there would be another issue, which is that if one takes a protein or other compound which has been shown to exhibit binding to a particular receptor, and attaches another substituent to it, loss of activity often results. Thus, even if applicants had provided a list of "target tissues", and an accompanying list of specific "binding molecules" which had been shown (by applicants or by others) to bind to the target tissue in question, the reality is that attaching, e.g., an aryl alkyl sulfenate to that "binding molecule" is likely to result in elimination of binding efficacy.

Thus, for each of several reasons, one of skill cannot "predict" accumulation of the compounds in a target tissue (as required by e.g., claim 16), and one cannot "predict" efficacy in the photosensitization of the target tissue even if accumulation could be achieved. The specification provides no "working examples" of a compound (falling with the scope of the claimed invention) which can be used in accordance with

the claimed invention. And the specification provides no guidance as to which "binding molecules" could be used or should be used for a given target tissue. Accordingly, "undue experimentation" would be required to practice the claimed invention.

✧

Claims 15-46 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- Claim 15 now recites (last 3 lines of the claim) that the target tissue is exposed to light such that the tissue itself is "photosensitized". What are the manifestations of a tissue that has been "photosensitized"...?

- Claim 15 is indefinite as to the meaning of a "carbohydrate receptor binding molecule", and for that matter, a "carbohydrate receptor". As a preliminary matter, it is suggested that applicants provide a few examples of a "carbohydrate receptor", and at least one example of a compound that will bind thereto. This will form the basis for further discussion.

- Claim 29 recites that "E is associated" with one of the recited biomolecules. What is meant by this? Does this mean that "E" must be present as a complex with one of the recited biomolecules at the time of administration, or does it mean that when "E" is administered (unattached to the sulfenate) to a mammal, that "E" forms a non-covalent association with one of the biomolecules, or is something else intended? What is meant by the assertion that (e.g.) a somatostatin receptor binding molecule is "associated" with a polyol, or that a steroid receptor binding molecule is "associated" with a nucleoside?

- Claim 29 recites that "E" can be "associated" with a dendrimer. One interpretation of this embodiment is that the claimed sulfenate compound is not administered as such, but rather is administered as a conjugate of the dendrimer, such that "E" is

bonded to an erstwhile nucleophilic group on the dendrimer. If this is the intention, claim 29 should be written in independent form, and the claim made clear that a conjugate is intended.

- Claim 30 recites that the amount which is "administered to the target tissue" can be as high as 500 mg/kg body weight. What is meant by this? There are principally two interpretations: (a) a quantity of 500 mg/kg body weight is administered to the subject, and whatever amount of the sulfenate that happens to make it to the target tissue is what ultimately gets there, or (b) as much of the sulfenate must be administered as is necessary to reach a concentration of 500 mg/kg within the tissue. Which of these is intended? The same issue applies in the case of claims 31, 40 and 41. Claims 33 and 43 are even more confusing. Are applicants asserting that the intact formulation must com into contact with the target tissue?

- Several of the claims (e.g., claims 30-33, 40, 41, 43) recite the qualifier "about" in reference to a range, e.g, "about 0.1 mg/kg to about 500 mg/kg". However, this renders the claims indefinite as to the upper and lower limits on the range. It is suggested that "about" be deleted at every occurrence.

- Claims 32-36 and 42-46 imply that the sulfenate is being administered as a composition. However, the independent claims (on which they depend) do not suggest or imply that the sulfenate is administered in this way. Accordingly, the claim dependence is improper. Claims 32-36 and 42-46 should be written in independent form.

✧

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell, can be reached at (571)272-0974. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

DAVID LUKTON
PATENT EXAMINER
GROUP 1800